



(19) Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11) EP 0 741 188 A3

(12) EUROPEAN PATENT APPLICATION

(88) Date of publication A3:  
14.07.1999 Bulletin 1999/28

(51) Int. Cl.<sup>6</sup>: C12N 15/17, C12N 5/10,  
C07K 14/62, A61K 38/28,  
A61K 48/00

(43) Date of publication A2:  
06.11.1996 Bulletin 1996/45

(21) Application number: 96303133.1

(22) Date of filing: 03.05.1996

(84) Designated Contracting States:  
AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL  
PT SE

Designated Extension States:  
AL LT LV SI

(30) Priority: 05.05.1995 US 435762  
05.05.1995 US 435503

(71) Applicant: ELI LILLY AND COMPANY  
Indianapolis, Indiana 46285 (US)

(72) Inventors:

- Chance, Ronald Eugene  
Westfield, Indiana 46074 (US)

- Dimarchi, Richard Dennis  
Carmel, Indiana 46033 (US)
- Hoffmann, James Arthur  
Greenwood, Indiana 46143 (US)
- Long, Harlan Beall  
Carmel, Indiana 46032 (US)
- Miller, Anne Reifel  
Indianapolis, Indiana 46208 (US)

(74) Representative:  
Hudson, Christopher Mark et al  
Lilly Industries Limited  
European Patent Operations  
Erl Wood Manor  
Windlesham Surrey GU20 6PH (GB)

(54) Single chain insulin with high bioactivity

(57) The instant invention provides polypeptide compounds of the formula b-BP-a having significant insulin activity, nucleotide sequences encoding said polypeptides, vectors comprising said nucleotide sequences, and cell lines transformed with said vectors useful for treating diabetes.

EP 0 741 188 A3



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number  
EP 96 30 3133

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
P,X	WO 95 16708 A (NOVO NORDISK A/S (DK); KRISTENSEN C.; KJELDSEN T.; ANDERSEN A.) 22 June 1995 * the whole document * ---	1-4,6-8, 10,11	C12N15/17 C12N5/10 C07K14/62 A61K38/28 A61K48/00
E	US 5 840 542 A (MOGAN BIOTECHNOLOGY RESEARCH INSTITUTE (KR); KANG YUP; YOON JI-WON) 24 November 1998 * table 1 * ---	1-3,5-11	
X	EP 0 068 701 A (CANADIAN PATENTS AND DEVELOPMENT LIMITED (CA); NARANG S.A.; WU R.J.) 5 January 1983 * page 5 * * page 13 - page 16 * * page 19 - page 20; claims * ---	1-3,5-11	
Y	STEWART C. ET AL.: "Insulin delivery by somatic cell gene therapy" JOURNAL OF MOLECULAR ENDOCRINOLOGY, vol. 11, 1993, pages 335-341, XP002912202 * abstract * ---	12	
X	EP 0 195 691 A (NOVO INDUSTRI A/S (DK); THIM L.; NORRIS K.; HANSEN M.T.) 24 September 1986 * page 13; table 1 * ---	1-3,6-8, 10,11	C12N C07K A61K
X	THIM L. ET AL.: "Secretion and processing of insulin precursors in yeast" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA, vol. 83, no. 18, September 1986, pages 6766-6770, XP002100937 * page 6768; table 1 * ---	1-3,6-8, 10,11	
		-/-	
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	27 April 1999	Macchia, G	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone	T : theory or principle underlying the invention		
Y : particularly relevant if combined with another document of the same category	E : earlier patent document, but published on, or after the filing date		
A : technological background	D : document cited in the application		
O : non-written disclosure	L : document cited for other reasons		
P : intermediate document	& : member of the same patent family, corresponding document		



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number  
EP 96 30 3133

DOCUMENTS CONSIDERED TO BE RELEVANT									
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)						
X	EP 0 163 529 A (NOVO INDUSTRI A/S (DK); MARKUSSEN FIIL AMMERER HANSEN THIM NORRIS VOIGT) 4 December 1985 * abstract * * page 10 * * page 13; table 1 * * page 32 - page 35; claims * ---	1-3,6-8, 10,11							
X	EP 0 427 296 A (NOVO NORDISK A/S (DK); MARKUSSEN FIIL AMMERER HANSEN THIM NORRIS VOIGT) 15 May 1991 * abstract * * page 7; table 1 * ---	1-3,6-8, 10,11							
P,X	EP 0 678 522 A (ELI LILLY CO (US); CHANCE R.E; DIMARCI R.D; FRANK B.H; SHIELDS J.E.) 25 October 1995 * abstract * * page 5 - page 6 * ---	1-3,6-8, 10,11							
E	GB 2 298 206 A (HANIL SYNTHETIC FIBER CO LTD (KR)) 28 August 1996 * abstract * ---	1,2,6-8, 10,11	TECHNICAL FIELDS SEARCHED (Int.Cl.6)						
A	NEWGARD C.B.: "Cellular engineering and gene therapy strategies for insulin replacement in diabetes" DIABETES, vol. 43, no. 3, 1 March 1994, pages 341-350, XP000571434 * the whole document * -----	12							
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>27 April 1999</td> <td>Macchia, G</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	27 April 1999	Macchia, G
Place of search	Date of completion of the search	Examiner							
THE HAGUE	27 April 1999	Macchia, G							
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... & : member of the same patent family, corresponding document							



European Patent  
Office

Application Number

EP 96 30 3133

### CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
  
- No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

### LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
  
- None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:



European Patent  
Office

LACK OF UNITY OF INVENTION  
SHEET B

Application Number  
EP 96 30 3133

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 4 totally; 1-3, 6-8, 10-12 all partially

A polypeptide compound of the formula b-BP-a, wherein b and a are the B and A chains of insulin, respectively, and BP is a bridging peptide, namely as in Seq.ID:2 and 4.  
Pharmaceutical formulation comprising said polypeptide.  
Nucleotide sequence encoding said polypeptide, vector comprising said nucleotide sequence, cell line transformed with said vector.

2. Claims: 5, 9 totally; 1-3, 6-8, 10-12 all partially

As invention 1 but concerning Seq.ID:1,3,5

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 96 30 3133

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.  
 The members are as contained in the European Patent Office EDP file on  
 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-04-1999

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9516708	A	22-06-1995	AU	1272295 A	03-07-1995
US 5840542	A	24-11-1998		NONE	
EP 0068701	A	05-01-1983	CA	1204682 A	20-05-1986
			JP	58004800 A	11-01-1983
			US	4792602 A	20-12-1988
EP 0195691	A	24-09-1986	DK	129385 A	23-09-1986
			AT	69266 T	15-11-1991
			AU	586855 B	27-07-1989
			AU	5500586 A	25-09-1986
			DE	3682303 A	12-12-1991
			DK	125786 A,B,	17-11-1986
			FI	861198 A,B,	23-09-1986
			GR	860764 A	21-07-1986
			IE	58842 B	17-11-1993
			JP	1923989 C	25-04-1995
			JP	6048993 B	29-06-1994
			JP	61221200 A	01-10-1986
			JP	2092913 C	18-09-1996
			JP	6133777 A	17-05-1994
			JP	8008871 B	31-01-1996
			JP	2553326 B	13-11-1996
			JP	8023985 A	30-01-1996
			PT	82241 A,B	01-04-1986
EP 0163529	A	04-12-1985	AT	66490 T	15-09-1991
			AT	143374 T	15-10-1996
			AU	590197 B	02-11-1989
			AU	4309285 A	05-12-1985
			CA	1304022 A	23-06-1992
			DE	3583824 A	26-09-1991
			DE	3588125 D	31-10-1996
			DK	238585 A,B,	01-12-1985
			DK	323687 A,B,	25-06-1987
			EP	0427296 A	15-05-1991
			FI	852135 A,B,	01-12-1985
			GR	851304 A	25-11-1985
			IE	66387 B	27-12-1995
			IE	80630 B	21-10-1998
			JP	1907704 C	24-02-1995
			JP	6030613 B	27-04-1994
			JP	61001389 A	07-01-1986
			JP	2084771 C	23-08-1996
			JP	6141866 A	24-05-1994

EPO FORM P055

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 96 30 3133

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.  
 The members are as contained in the European Patent Office EDP file on  
 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-04-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0163529 A		JP 7121226 B JP 2011125 C JP 6141865 A JP 7046998 B JP 2519023 B JP 7309896 A NO 174351 B PT 80551 A,B US 4916212 A	25-12-1995 02-02-1996 24-05-1994 24-05-1995 31-07-1996 28-11-1995 10-01-1994 01-06-1985 10-04-1990
EP 0427296 A	15-05-1991	AT 66490 T AT 143374 T AU 590197 B AU 4309285 A CA 1304022 A DE 3583824 A DE 3588125 D DK 238585 A,B, DK 323687 A,B, EP 0163529 A FI 852135 A,B, GR 851304 A IE 66387 B IE 80630 B JP 1907704 C JP 6030613 B JP 61001389 A JP 2084771 C JP 6141866 A JP 7121226 B JP 2011125 C JP 6141865 A JP 7046998 B JP 2519023 B JP 7309896 A NO 174351 B PT 80551 A,B US 4916212 A	15-09-1991 15-10-1996 02-11-1989 05-12-1985 23-06-1992 26-09-1991 31-10-1996 01-12-1985 25-06-1987 04-12-1985 01-12-1985 25-11-1985 27-12-1995 21-10-1998 24-02-1995 27-04-1994 07-01-1986 23-08-1996 24-05-1994 25-12-1995 02-02-1996 24-05-1994 24-05-1995 31-07-1996 28-11-1995 10-01-1994 01-06-1985 10-04-1990
EP 0678522 A	25-10-1995	AT 133961 T AU 630912 B AU 4922690 A BG 60769 B CA 2009579 A CN 1044820 A,B CN 1148984 A	15-02-1996 12-11-1992 16-08-1990 29-02-1996 09-08-1990 22-08-1990 07-05-1997

**ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.**

EP 96 30 3133

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.  
 The members are as contained in the European Patent Office EDP file on  
 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

27-04-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0678522 A		DE 69025210 D DK 383472 T EP 0383472 A ES 2083424 T FI 95915 B GR 3019501 T HK 60296 A HU 212679 B HU 9500171 A IE 73251 B IL 93282 A JP 2110045 C JP 2264798 A JP 8022878 B LU 88830 A LU 88831 A LV 10291 A,B MX 19389 A NO 179587 B NO 950721 A PT 93057 A,B US 5514646 A US 5700662 A	21-03-1996 06-05-1996 22-08-1990 16-04-1996 29-12-1995 31-07-1996 12-04-1996 30-09-1996 28-08-1995 21-05-1997 31-08-1995 21-11-1996 29-10-1990 06-03-1996 06-01-1997 10-01-1997 20-10-1994 28-02-1994 29-07-1996 10-08-1990 31-08-1990 07-05-1996 23-12-1997
GB 2298206 A	28-08-1996	KR 150565 B DE 19605657 A FR 2730495 A JP 8333395 A	17-08-1998 22-08-1996 14-08-1996 17-12-1996